cefmetazole per milligram of sample as follows:

$$\text{Micrograms of cefmetazole per milligram} = \frac{A_u \times P_s \times 100}{A_s \times C_u \times (100 - m)}$$

where:

A_u=Area of the cefmetazole peak in the chromatogram of the sample (at a retention time equal to that observed for the standard);

A_s=Area of the cefmetazole peak in the chromatogram of the cefmetazole working standard;

P_s=Cefmetazole activity in the cefmetazole working standard solution in micrograms per milliliter;

C_u=Milligrams of cefmetazole sample per milliliter of sample solution; and

m=Percent moisture content of the sample.

(B) *Cefmetazole content (milligrams of cefmetazole per container).* Calculate the cefmetazole content of the container as follows:

$$\text{Milligrams of cefmetazole per container} = \frac{A_u \times P_s \times d}{A_s \times 1{,}000}$$

where:

A_u=Area of the cefmetazole peak in the chromatogram of the sample (at a retention time equal to that observed for the standard);

A_s=Area of the cefmetazole peak in the chromatogram of the cefmetazole working standard;

P_s=Cefmetazole activity in the cefmetazole working standard solution in micrograms per milliliter; and

d=Dilution factor of the sample.

(2) *Sterility.* Proceed as directed in § 436.20 of this chapter, using the method described in § 436.20(e)(1).

(3) *Bacterial endotoxins.* Proceed as directed in the United States Pharmacopeia bacterial endotoxins test.

(4) *Moisture.* Proceed as directed in § 436.201 of this chapter.

(5) *pH.* Proceed as directed in § 436.202 of this chapter, using an aqueous solution containing 100 milligrams per milliliter.

(6) *Identity.* Proceed as directed in § 436.211 of this chapter using a mineral oil mull prepared as described in § 436.211(b)(2).

[55 FR 6634, Feb. 26, 1990]

§ 442.80 Cefprozil.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Cefprozil is an approximate 9:1 mixture of the Z (cis) and the E (trans) isomers, respectively, of (6*R*,7*R*)-7-[(*R*)-2-amino-2-(*p*-hydroxyphenyl)acetamido]8-oxo-3-propenyl-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid. It is so purified and dried that:

(i) Its potency is not less than 900 micrograms nor more than 1,050 micrograms of cefprozil activity per milligram, on an anhydrous basis.

(ii) The ratio of its (E) isomer to total cefprozil is not less than 0.06 nor more than 0.11.

(iii) Its moisture content is not less than 3.5 percent nor more than 6.5 percent.

(iv) The pH of an aqueous solution containing 5 milligrams per milliliter is not less than 3.5 nor more than 6.5.

(v) It is crystalline.

(vi) It gives positive identity tests.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for cefprozil potency, E isomer to total cefprozil ratio, moisture, pH, crystallinity, and identity.

(ii) Samples, if required by the Director, Center for Drug Evaluation and Research: 10 packages, each containing approximately 500 milligrams.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed in § 436.216 of this chapter, using ambient temperature, an ultraviolet detection system operating at a wavelength of 280 nanometers, a 25 centimeter × 3.9 to 4.6 millimeter (id) column packed with microparticulate (5 to 10 micrometers in diameter) reversed phase packing material such as octadecyl silane bonded to silicas, a flow rate of 1.0 milliliter per minute, and a known injection volume of 10 microliters. The retention time for cefprozil (Z) is between 4 and 6 minutes and the retention time for cefprozil (E) is between 6 and 8 minutes. Mobile phase, working standard

and sample solutions, system suitability requirements, and calculations are as follows:

(i) *Mobile phase.* Dissolve 20.7 grams of ammonium phosphate, monobasic in 1,800 milliliters of water and adjust the pH to 4.4 with phosphoric acid, if necessary. Add 200 milliliters of acetonitrile and mix. Filter the mobile phase through a suitable filter capable of removing particulate matter 0.5 micron in diameter and degas it just prior to its introduction into the chromatograph. The proportion of acetonitrile may be modified in the range of 6 to 14 percent to obtain the desired retention times. Increasing the amount of acetonitrile will decrease both the retention times and the separation between the isomers, whereas, decreasing the amount of acetonitrile will increase retention times and the separation between the isomers.

(ii) *Preparation of working standard solutions*—(A) *Cefprozil (Z) working standard solution.* Accurately weigh approximately 12.5 milligrams of the cefprozil (Z) working standard into a 50-milliliter volumetric flask. Dilute to volume with water and shake the flask vigorously until the solute dissolves completely. Use this solution within 6 hours.

(B) *Cefprozil (E) working standard solution.* Accurately weigh approximately 12.5 milligrams of the cefprozil (E) working standard into a 50-milliliter volumetric flask. Dilute to volume with water and shake the flask vigorously until the solute dissolves completely. Pipet 5 milliliters into a 50-milliliter volumetric flask, dilute to volume with water and mix thoroughly. Use this solution within 6 hours.

(iii) *Sample solution.* Accurately weigh approximately 15 milligrams of sample into a 50-milliliter volumetric flask. Dilute to volume with water and shake the flask vigorously until the solute dissolves completely. Use this solution within 6 hours.

(iv) *System suitability requirements*—(A) *Asymmetry factor.* The asymmetry factor (A_S)is satisfactory if it is not less than 0.9 and not more than 1.1 for the cefprozil (Z) response.

(B) *Efficiency of the column.* The absolute efficiency (h_r) is satisfactory if it is not more than 10 for the cefprozil (Z) response.

(C) *Resolution factor.* The resolution factor (R) between the response for cefprozil (Z) and the response for cefprozil (E) is satisfactory if it is not less than 2.5.

(D) *Coefficient of variation (Relative standard deviation).* The coefficient of variation ($S_R$of 5 replicate injections of the cefprozil (Z) reference solution response) is satisfactory if it is not more than 2.0 percent.

(E) *Capacity factor (k').* The capacity factor (k') for cefprozil (Z) is satisfactory if it is not less than 0.7 and not more than 1.1. If the system suitability parameters have been met, then proceed as described in § 436.216(b) of this chapter.

(v) *Calculations.* Calculate the micrograms of cefprozil per milligram of sample on an anhydrous basis as follows:

$$\text{Micrograms of cefprozil (Z) or cefprozil (E) per milligram (as is)} = \frac{A_u \times P_s}{A_s \times C_u}$$

$$\text{Micrograms of cefprozil per milligram (as is)} = \text{cefprozil (Z)} + \text{cefprozil (E)}$$

$$\text{Micrograms of cefprozil per milligram (Anhydrous)} = \frac{\text{cefprozil potency (as is)} \times 100}{(100 - m)}$$

where:

A_U = Area of the cefprozil (Z) or cefprozil (E) response in the chromatogram of the sample (at a retention time equal to that observed for the standard);

A_S = Area of the cefprozil (Z) or cefprozil (E) response in the chromatogram of the cefprozil (Z) or the cefprozil (E) working standard ;

P_S = Cefprozil (Z) or cefprozil (E) activity in the cefprozil (Z) or the cefprozil (E) working standard solution in micrograms per milliliter;

C_U = Milligrams of sample per milliliter of sample solution; and

m = Percent moisture content of the sample.

(2) *Cefprozil (E)/cefprozil ratio.* Using the procedure described in paragraph (b)(1) of this section calculate the cefprozil (E)/cefprozil ratio as follows:

$$\text{Trans ratio} = \frac{\text{cefprozil (E) (mcg/mg, as is)}}{\text{cefprozil (mcg/mg, as is) Total}}$$

(3) *Moisture.* Proceed as directed in § 436.201 of this chapter.

(4) *pH.* Proceed as directed in § 436.202 of this chapter, using a carbon dioxide free aqueous solution containing 5 milligrams of cefprozil per milliliter.

(5) *Crystallinity.* Proceed as directed in § 436.203(a) of this chapter.

(6) *Identity*—(i) *Infrared.* Proceed as directed in § 436.211 of this chapter, using a 1.0 percent potassium bromide disc prepared as described in paragraph (b)(1) of that section.

(ii) *High performance liquid chromatography (HPLC).* The HPLC retention times for the responses of the cefprozil isomers in the assay preparation of the sample must be within 2 percent of the HPLC retention times of the responses of the corresponding cefprozil working standards.

[58 FR 26660, May 4, 1993]

Subpart B—Oral Dosage Forms

§ 442.104 Cefaclor monohydrate oral dosage forms.

§ 442.104a Cefaclor monohydrate capsules.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Cefaclor monohydrate capsules are composed of cefaclor monohydrate and one or more suitable and harmless lubricants and diluents enclosed in a gelatin capsule. Each capsule contains cefaclor monohydrate equivalent to either 250 milligrams or 500 milligrams of cefaclor. Its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of cefaclor that it is represented to contain. Its moisture content is not more than 8.0 percent. The cefaclor monohydrate used conforms to the standards prescribed by § 442.4(a)(1).

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The cefaclor monohydrate used in making the batch for potency, moisture, pH, identity, and crystallinity.

(*b*) The batch for potency and moisture.

(ii) Samples required:

(*a*) The cefaclor monohydrate used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The batch: A minimum of 30 capsules.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed in § 442.40(b)(1)(ii) of this chapter, except prepare the working standard and sample solutions and calculate the potency of the sample as follows:

(i) *Preparation of working standard solution.* Dissolve and dilute an accurately weighed portion of the cefaclor working standard in sufficient 0.1*M* potassium phosphate buffer, pH 4.5 (as described in § 436.101(a)(4) of this chapter) to obtain a concentration of 1 milligram of cefaclor per milliliter.

(ii) *Preparation of sample solution.* Place one capsule into a high-speed glass blender jar containing sufficient 0.1*M* potassium phosphate buffer, pH 4.5 (as described in § 436.101(a)(4) of this chapter) to obtain a concentration of 1 milligram of cefaclor per milliliter. Filter a portion to be used through a 10-micron filter.

(iii) *Calculations.* Calculate the cefaclor content in milligrams per capsule as follows:

$$\text{Milligrams of cefaclor per capsule} = \frac{A_u \times P_a \times d}{A_s \times 1{,}000}$$

where:

A_u = Absorbance of sample solution;

P_a = Potency of working standard in micrograms per milliliter;

A_s = Absorbance of working standard solution;

d = Dilution factor of the sample.

(2) *Moisture.* Proceed as directed in § 436.201 of this chapter.

[46 FR 3833, Jan. 16, 1981; 46 FR 21360, Apr. 10, 1981]

§ 442.104b Cefaclor monohydrate for oral suspension.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Cefaclor monohydrate for oral suspension is cefaclor monohydrate with one or more suitable